REMARKS/ARGUMENTS

Claims 1-4 and 9-11 have been amended solely for greater clarity. Support for the claim amendments can be found throughout the specification(e.g., pages 35-37). Claims 22-25 have been added. Support for the new claims can be found in the specification (e.g., page 4, lines 2-24; and Example 11 on pages 52-53) and original claims (e.g., claims 9 and 14). No new matter is introduced in any of the above amendments. These amendments have been made solely to expedite prosecution of the application. Applicants reserve the right to pursue claims of similar or differing scope in the future.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim Rejections under 35 U.S.C. 103(a)

The Examiner has rejected claims 1-4, 8-11, 14, and 19-21 as being allegedly obvious over Uchida et al. (U.S. 6,150,092) in view of Robinson et al. (WO 95/04142), Agrawal et al. (PNAS, 94:2620-2625, 1997), and Bennett et al. (U.S. 5,998,148). Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants reiterate the arguments already made of record and contend that the cited references do not render the claims obvious. Nevertheless, solely to expedite prosecution of the application, Applicants have amended claims 1-4 and 19 for greater clarity, and have amended claims 9-11 to more particularly point out the claimed invention. Applicants have added new claims 22-25 to include the subject matter which has been canceled from independent claim 9. As described above, support for any of these amendments can be found in the original specification.

According to the Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (Federal Register Vol. 72, No. 195 at pages 57,526-57,535) (effective October 10, 2007) ("the Guidelines"), a § 103 claim rejection based on a purported teaching, suggestion or motivation to combine prior art references to arrive at the claimed invention must support a conclusion of obviousness by including: (1) a finding that there was some teaching, suggestion or motivation

to modify or combine the cited references; (2) a finding that there was a reasonable expectation of success; and (3) whatever additional findings based on the *Graham* factual inquiries may be necessary in view of the specific facts. Moreover, according to the Guidelines (page 57,534):

> If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. The courts have made clear that the teaching, suggestion or motivation test is flexible and an explicit suggestion to combine the prior art is not necessary. The motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art, or, in come cases, from the nature of the problem to be solved.

As stated by the Supreme Court in *KSR International Co. v. Teleflex Inc.* (550 U.S. __, 82 U.S.P.Q.2d 1385 (2007)) ("*KSR*"), the framework for analyzing obviousness under § 103 remains that which was stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) ("*Graham*") and includes the familiar *Graham* factor analysis referred to in the Guidelines above. Here, in view of the *Graham* factors, the Examiner has provided no rational basis, explicit or implicit, to support a legal finding of obviousness under § 103 in view of the cited references, as required by *KSR* (550 U.S. __, 82 U.S.P.Q.2d at 1396 (2007)).

Moreover, putting improper combinations aside, even were the skilled worker to have sought to combine the cited references (for which there is no rational basis) -- that combination would still not result in the claimed invention because the combined teachings fail to teach or suggest all of the claim limitations of the pending claims.

First of all, Applicants submit that the Examiner has not satisfied the requirement of establishing a *prima facie* case of obviousness against independent claims 1 and 8, which require a distinct and specific nucleotide sequence of SEQ ID NO: 34 (*modified* form of SEQ ID NO: 2). The Examiner acknowledged that Uchida et al. neither teach SEQ ID NO: 2 (unmodified form) nor SEQ ID NO: 34 (modified form). However, the Examiner seems to have made a conclusory statement that SEQ ID NO: 2 (*unmodified* form) is rendered obvious by Uchida et al., without articulated reasoning with some rational underpinning to support this legal conclusion of obviousness. For example, the Examiner asserts that "[t]he antisense oligonucleotides claimed by Uchida et al. are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO: 7. It is noted that antisense oligonucleotides of the instant application, including claimed

SEQ ID NO: 34 (modified version of SEQ ID NO: 2) as well as SEQ ID NOS: 2, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 28, and 29, for example, are all targeted to SEQ ID NO:7 of Uchida et al, and further all the antisense oligonucleotides of the instant application either overlap, embrace, or are embraced by the specifically claimed antisense of Uchida et al claim 7, for example (SEQ ID NOS: 51, 54, 53, 50, 49, 138, and 141 of Uchida et al, for example)." See Office Action, page 3, lines 12-20.

The "core regions" disclosed in Uchida et al. are not limited to SEQ ID NO: 7. Rather, Uchida's core regions span at least about 500 nucleotides in the VEGF gene, including regions within the 383-position or thereabout to the 521-position or thereabout in SEQ ID NO:1" (see the paragraph bridging columns 20 and 21). Uchida's core regions also include regions within the 77- to 570-positions in SEQ NO: 1, the nucleotide sequences of from the 95- to 108-positions (SEQ ID NO:2), 149- to 174-positions (SEQ ID NO:3), 185- to 210-positions (SEQ ID NO:4), 219- to 244-positions (SEQ ID NO:5), 254- to 276-positions (SEQ ID NO:6), 287- to 328-positions (SEQ ID NO:7), 357- to 372-positions (SEQ ID NO:8), 389- to 534-positions (SEQ ID NO:9), SEQ ID NOS:2, 4, 5, 6, 7, and 9 (see column 21, lines 34-49).

Although Uchida et al. list hundreds of oligonucleotides within the above-mentioned core regions, Uchida et al. do not show that any oligonucleotide targeted to certain regions of VEGF was reasonably likely to be useful. In fact, Uchida et al. show that some oligonucleotides that either overlap, embrace, or are embraced in these so-called "core" regions are ineffective in their assay. For example, although SEQ ID NO: 51 overlaps with SEQ ID NO: 7, it is a weak or ineffective inhibitor of VEGF expression as assayed in cells (Table 9). Prior to Applicant's findings, no one had characterized Applicant's SEQ ID NO: 2 because it did not previously exit. This sequence could not have been predicted merely by knowing about Uchida's core regions, nor could the functional properties of this sequence be determined by simply comparing them with allegedly similar sequence structure. It is evident from Uchida's own data that similar sequences are not correlated with the same efficacy. For example, although SEQ ID NOs: 141 and 142 overlap, they differ significantly in inhibiting VEGF expression (see Table 2; and below).

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SEQ ID NO: 141:        CACACAGGATGGCT     9%  expression
SEQ ID NO: 142:     GGCACACAGGATGG        38% expression
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Uchida et al. fail to provide sufficient guidance or motivation for one of skill in the art to identify or design SEQ ID NO: 2 (*unmodified* form). None of the other cited references, taken alone or in combination, suggests or motivates the skilled artisan to design this particular sequence. Uchida's disclosure of certain core sequences amidst a number of ineffective sequences and hundreds of unknowns surely falls far short of providing one skilled in the art with a reasonable expectation of success. This is particular true in light of the unpredictability of antisense technology at the time this application was filed (see, e.g., Agrawal et al., Mol. Medicine Today (2000), 6:72-81, an abstract is enclosed as **Exhibit A**). By contrast, it is Applicants' discovery that SEQ ID NO: 2 (unmodified and modified forms) effectively inhibits tumor growth or angiogenesis in both in vitro and in vivo assays carried out in a variety of tumors (e.g., Kaposi' sarcoma, ovarian carcinoma, melanoma, prostate carcinoma, and pancreatic carcinoma).

Further, the Examiner admits that Uchida et al. do not disclose the 2' O-methyl modifications of SEQ ID NO: 34, the specific cells of claim 7, or chemotherapeutic agents included in a composition comprising a VEGF antisense (Office Action, page 4, lines 11-13). However, the Examiner alleges that the 2' O-methyl modifications are disclosed by Robinson et al., that Agrawal et al. have taught the same modification used in SEQ ID NO: 34, and that Bennett et al. teach many modifications as well as liposome delivery (see Office Action, page 4, lines 14-22; and page 5, lines 1-10).

As described above, Uchida et al. do not teach or suggest each of the elements required by the instant claims – at least with respect to the sequence of SEQ ID NO: 2 (*unmodified* form). In the absence of any guidance for designing the sequence of SEQ ID NO: 2, one of ordinary of skill in the art could not possibly be motivated to modify this sequence to arrive at SEQ ID NO: 34, a particular modified form of SEQ ID NO: 2. Accordingly, the Examiner has not satisfied the requirement of establishing a *prima facie* case of obviousness against independent claims 1 and 8.

Second, Applicants submit that the Examiner has not satisfied the requirement of establishing a *prima facie* case of obviousness against independent claims 9 and 22 which are directed to methods for inhibiting tumor growth and angiogenesis. Since claims 9 and 22 require

the specific sequence of SEQ ID NO: 34, these two claims are not rendered obvious by the cited references for the same reasons as described above.

In addition, Applicants respectfully point out that claims 9 and 22 have unique technical features (besides the sequence of SEQ ID NO: 34) which are not obvious over the cited prior art. For example, claim 9 relates to a method for inhibiting tumor growth in vivo, wherein said tumor is selected from ovarian carcinoma, melanoma, Kaposi's sarcoma, prostate carcinoma and pancreatic carcinoma. Claim 22 relates to a method for inhibiting angiogenesis in vivo. By contrast, Uchida et al. only disclose methods of testing the antisense probes to inhibit VEGF expression in vitro. Uchida et al. do not provide any enabling or meaningful disclosure of a method of inhibiting tumor growth in vivo or inhibiting angiogenesis in vivo. In addition, although Uchida et al. generally mention that the antisense nucleic acid compound can be used as an anticancer drug to inhibit the growth of solid tumors, Uchida et al. are absolutely silent on a tumor selected from ovarian carcinoma, melanoma, Kaposi's sarcoma, prostate carcinoma and pancreatic carcinoma. None of the other cited references bridge the gap between Uchida et al. and the claimed invention. Accordingly, the cited references in combination still fail to render obvious all elements of claim 9 or 22.

Further, Applicants submit that the cited references do not provide any motivation for one of ordinary skill in the art to practice the claimed methods. Uchida et al. describe that antisense probes are effective in decreasing VEGF expression in cell-free assays. Although Uchida et al. briefly describe cell-based assays with PS-modified forms of antisense probes, these PS-modified probed did not work well in cells (see Table 9). The ineffectiveness of the probes of Uchida et al. in cells would not motivate a skilled artisan to inhibit tumor growth or angiogenesis in vivo – it actually would teach away from the claimed methods. In addition, there was no reasonable success in carrying out the vivo treatment methods as recited in claims 9 and 22, particularly in view of the unpredictability of antisense technology. Accordingly, the Examiner has not satisfied the requirement of establishing a *prima facie* case of obviousness against independent claims 9 and 22.

In sum, Applicants submit that all of the pending claims are non-obvious in view of Uchida et al. Furthermore, since none of the defects of Uchida et al. are cured by the other cited references, Applicants assert that the claims are not obvious in view of all cited references.

Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000. If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945,** under Order No. **VASG-P03-003**.

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Respectfully submitted,

By _____
Z. Angela Guo
Registration No.: 54,144
FISH & NEAVE IP GROUP, ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant

EXHIBIT A

1: Mol Med Today. 2000 Feb;6(2):72-81.

Erratum in:
Mol Med Today 2000 Mar;6(3):103.

Antisense therapeutics: is it as simple as complementary base recognition?

Agrawal S, **Kandimalla ER**.

Hybridon, 155 Fortune Boulevard, Milford, MA 01757, USA.
sagrawal@hybridon.com

Antisense oligonucleotides provide a simple and efficient approach for developing target-selective drugs because they can modulate gene expression sequence-specifically. Antisense oligonucleotides have also become efficient molecular biological tools to investigate the function of any protein in the cell. As the application of antisense oligonucleotides has expanded, multiple mechanisms of oligonucleotides have been characterized that impede their routine use. Here, we discuss different mechanisms of action of oligonucleotides and the possible ways of minimizing non-antisense-related [corrected] effects to improve their specificity.

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